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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,418	05/10/2002	Daniel Sauder	55908-2003200	8778

38706 7590 01/25/2005

FOLEY & LARDNER LLP
THREE PALO ALTO SQUARE
3000 EL CAMINO REAL
SUITE 100
PALO ALTO, CA 94306

EXAMINER	
BELYAVSKYI, MICHAIL A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,418	SAUDER ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *39-46 and 50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38 and 47-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/28/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment, filed 11/19/04 is acknowledged.

Claims 1-50 are pending.

1. Applicant's election with traverse of Group I, claims 1-38 and 47-49 in Response to Restriction Requirement, filed on 11/19/04 is acknowledged. Applicant traverse the Restriction Requirement on the grounds that the inventions must be both independent and distinct and an undue search burden on the examiner. However, MPEP 803 states that the Inventions be either independent or distinct and a burden on the Examiner if restriction is required.

Regarding applicant's comments about undue burden, the MPEP 803 (August 2001) states that "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification separate status in the art, or a different field of search". The Restriction Requirement enunciated in the previous Office Action meets this criteria, indicates that inventions recognized divergent subject matter and that a different field of search would be required based upon the structurally distinct products recited and the various methods of use comprising distinct method steps. Moreover, a prior art search also requires a literature search. All the above establishes that serious burden is placed on the examiner by the examination of more than one Group. The Inventions are distinct for reasons elaborated in the previous Office Action and above.

The requirement is still deemed proper and is therefore made FINAL.

Claims 39-46 and 50 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 1-38 and 47-49 drawn to a method of treatment or prophylaxis of an IL-10 deficiency-mediated disease and a method for increasing IL-10 levels in the blood or tissue of a mammalian patient, each comprising administering blood cells which has been treated ex vivo with a stressor wherein stressor is oxidative conditions , ultraviolet radiation or thermal stress are under consideration in the instant application.

2. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Canada on 05/11/2000. It is noted, however, that applicant has not filed a copy of the 2,308,105 application as required by 35 U.S.C. 119(b).

3. Applicant is advised that should claims 36-38 be found allowable, claims 47-49 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

4. The following is a quotation of the second paragraph of 35 U.S.C. 112.
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 1 –35 are indefinite and ambiguous in the recitation of " IL-10 deficiency-mediated disorder". The characteristics and metes and bounds of said "IL-10 deficiency-mediated disorder" are unclear , indefinite, not defined by the claims and the specification. Moreover, there is no art recognize terms " IL-10 deficiency-mediated disorder".

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-38 and 47-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the limited working examples, the unpredictability in

the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification only discloses a contact hypersensitivity (CHS) test on Balb/c mice wherein suppression of CHS has been detected in mice challenged with DNFB and subsequently injected with an aliquot of blood which has been *ex-vivo* treated with a stressor (see Example 1-3 in particular).

The specification does not adequately teach how to effectively treat , prophylaxis and prevent any IL-10 deficiency-mediated disease, including pemphigus in a patient, or increase the levels of IL-10 in the blood and/or tissue of a mammalian patient by administering an effective amount of stressed mammalian blood cells wherein said blood cells have been extracorporeally subjected to both oxidative conditions and UV radiation. There is no art recognized definition of "IL-10 deficiency-mediated disease" and the specification does not define what disease are considered to be "IL-10 deficiency-mediated". The specification only disclosed that if after administration of IL-10 from external source, there would be no symptoms of the disorder than said disorder is IL-10 deficiency-mediated (see page 7, lines 3-12 of the instant specification in particular). Moreover, no animals models were used to study the effectively of prophylaxis, preventing or therapeutic treatment of any IL-10 deficiency-mediated disease, including pemphigus in a patient, or increase the levels of IL-10 in the blood and/or tissue of a mammalian patient by administering an effective amount of stressed mammalian blood cells wherein said blood cells have been ex-vivo treated with a stressor. Since there is no animal model studies and data in the specification to show the effectively of treatment or prophylaxis of any IL-10 deficiency-mediated disease, including pemphigus in a patient, or increase the levels of IL-10 in the blood and/or tissue of a mammalian patient comprising administering to the patient an effective amount of stressed mammalian blood cells it is unpredictable how to correlate a contact hypersensitivity (CHS) test on Balb/c mice with claimed *in vivo* use. Lalani et al. (Annals of Allergy Asthma & Immunol., 1997, V.79, pages 469-484), teach IL-10 is a molecule whose role in the immune system is still under study. The effects of IL-10 depend on many factors not all of which are understood. Much of our knowledge of IL-10 is obtained from in vitro or animal studies. Though valuable, these studies have limitation in extrapolating their effects on human system (see entire document, page 478 in particular). Mestas et al (J. of Immunology, 2004, 172, pages 2731-238) teach that there exist significant differences between mice and humans in immune system development, activating and response to challenge in both the innate and adaptive arms. As therapies for human diseases become ever more sophisticated and specifically targeted it becomes increasing important to understand the potential limitations of extrapolating data from mice to humans. The literature is littered with the examples of therapies that work well in mice but fail to provide similar efficacy in humans. Feldman et al (Transplant. Proc. 1998, 30, 4126-4127) teach that "while it is not difficult to study the pathogenesis of animal models of disease, there are multiple constraints on analyses of the pathogenesis of human disease, leading to interesting dilemmas such as how much can we rely on and extrapolate from animal models in disease". Feldman et al ., further teach that in a

chronic immune-driven inflammatory response there are a number of pathways that become engaged and effective therapy in immune inflammatory diseases such as rheumatoid arthritis, will come from therapy aimed at several points in the disease pathway.

The specification does not provide sufficient teaching as to how it can be assessed that treatment or prophylaxis of any IL-10 deficiency-mediated disease, including pemphigus in a patient, or increase the levels of IL-10 in the blood and/or tissue of a mammalian patient was achieved after the administration of a therapeutically effective amount of stressed mammalian blood cells. Since the method of treatment or prophylaxis of any IL-10 deficiency-mediated disease, including pemphigus in a patient, or increase the levels of IL-10 in the blood and/or tissue of a mammalian patient, by administering an effective amount of stressed mammalian blood cells can be species- and model-dependent (see Van Noort et al. International Review of Cytology, 1998, v.178, pages 127-204, Table III in particular) , it is not clear that reliance on the contact hypersensitivity (CHS) test on Balb/c mice accurately reflects the relative mammal and human efficacy of the claimed therapeutic strategy. The specification does not teach how to extrapolate data obtained from the above discussed studies to the development of effective *in vivo* mammalian including human therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of a method of treatment or prophylaxis of any IL-10 deficiency-mediated disease, including pemphigus in a patient, or increase the levels of IL-10 in the blood and/or tissue of a mammalian patient, by administering an effective amount of stressed mammalian blood cells. Moreover, as has been discussed, supra one skill in the art would not know what are the diseases that are " IL-10 deficiency mediated. Thus in the absence of working examples or detailed guidance in the specification, the intended uses of any pharmaceutical composition comprising stressed mammalian blood cells are fraught with uncertainties.

Also an issue is whether or not the claimed method would function "for the prophylaxis or preventing of any IL-10 deficiency-mediated disease, including pemphigus in a patient. The nature of the invention is such that it would require the administration of blood cells that have been *ex vivo* treated with a stressor that would prevent a mammalian subject from having any IL-10 deficiency-mediated disease. The burden of enabling the prevention of a disease (i. e. the need for additional testing) would be greater than that of enabling a treatment due to the need to screen those humans susceptible to such diseases and the difficulty of proof that the administration of stressed blood cells was the agent that acted to prevent the condition. Further, the specification does not provide guidance as to how one skilled in the art would go about screening those patients susceptible to any IL-10 deficiency-mediated disease, including pemphigus within the scope of the presently claimed invention. Nor is guidance provided as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed compounds in preventing these disease states. Accordingly, undue experimentation is necessary to determine screening and testing protocols to demonstrate the efficacy of the presently claimed invention.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of treatment or prophylaxis of any any IL-10 deficiency-mediated disease, including pemphigus in a patient, or increase the levels of IL-10 in the blood and/or tissue of a mammalian patient each comprising administering an effective amount of stressed mammalian blood cells in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. Also an issue is that the incorporation of essential material in the specification by reference to Kondo et al. on page 14, Example 1 for a contact hypersensitivity test according to approved animal experimentation procedures is improper because an application for a patent when filed may incorporate "essential material" by reference to (1) a United States patent or (2) an allowed U.S. application, see MPEP 608.01(p),. "Essential material" is defined as that which is necessary to (1) support the claims, or (2) for adequate disclosure of the invention (35 U.S.C. 112). "Essential material" may not be incorporated by reference to (1) patents or applications published by foreign countries or regional patent offices, to (2) non-patent publications, to (3) a U.S. patent or application which itself incorporates "essential material" by reference or to (4) a foreign application. See In re Fouche, 169 USPQ 429; 439 F.2d 1237 (CCPA 1971).

Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-3, 5-10, 16-25, 36-38 and 47-49 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 00/06703 or by WO 98/07463 or by U.S. Patent No. 5,980,954 as is evidenced by the known fact disclosed in the Specification on page 1, lines 5-20.

The WO ' 703 teaches a method of treating inflammatory disease in a mammalian patient, including human comprises administering to the patient stressed mammalian blood cells (see the entire document Abstract in particular . The WO '703 teaches that stress blood cells have been extracting from the patient an aliquot of blood of volume, contacting the aliquot of blood, extracorporeally subject to at both oxidative conditions, ultraviolet radiation and heat stress simultaneously (see overlapping pages 5-6 and 7 in particular). The WO '703 teaches that oxidative environment, such as a mixture of ozone, wherein an ozone content from about 1 to about 100 μg/ml and oxygen bubbled through the blood aliquot, from about 0.5 to 60 min wherein said amount does not give rise to excessive levels of cell damage. The WO ' 703 teaches that the flow rate of the gas is applied at about 0.01-2 liters/min. The WO ' 703 teaches that a mixture of medical grade oxygen and ozone is bubbling through aliquot of blood. (see overlapping pages 7 –9 of the instant Specification in particular). The WO '703 teaches that the temperature stressor is in a range from about 40 to about 55° C, most preferable 42.5 ∓ 1^0C (see pages 8, 9 and 11 in particular). The WO '703 teaches that UV stessor is UV-c radiation (see page 8 in particular). Wherein the patient is human and the aliquot of modified mammalian blood is the patient's own blood , of volume from about 0.1-500 ml (page 7, in particular). The WO '703 teaches that the stressor can be applied from 0.5 – 60 minutes, most preferably about 3 minutes (see page 9, lines 5-30 in particular). The WO ' 703 teaches several means of administration of stressed blood cells including intravenously or intraperitoneal injection (see page 10, lines 25-35 in particular).

As evidence by the disclosure of the Specification on page 1, line 5-20, it was well known in the art at the time the invention was made that deficiency of IL-10 results in the development of inflammatory disease. Thus, it is apparent that a method of treating inflammatory disease in a mammalian patient, taught by WO'703 is a method for treatment of an IL-10 deficiency-mediated disease.

The WO ' 436 teaches a method of treating an autoimmune diseases in a mammalian patient, including inflammatory bowel disease and psoriasis, comprises administering to the patient stressed mammalian blood cells (see the entire document, pages 1, 17, and 23 in particular) . The WO ' 436 teaches that stress blood cells have been extracting from the patient an aliquot of blood of volume, contacting the aliquot of blood, extracorporeally subject to at both oxidative

conditions, ultraviolet radiation and heat stress simultaneously. (see overlapping pages 13-14 and 16-17 in particular). The WO ' 436 teaches that oxidative environment, such as a mixture of ozone, wherein an ozone content from about 1.0 to about 100 μg/ml and oxygen bubbled through the blood aliquot, from about 0.5 to 60 min (pages 14-15, in particular). The WO ' 436 teaches that the flow rate of the gas is applied at about 0.01-2 liters/min. (see page 15 of the instant specification in particular). The WO ' 436 teaches that the temperature stressor is in a range from about 0^0 to about 55° C (see page 14 in particular). The WO ' 436 teaches that UV stessor is UV-c radiation (see page 15 in particular). Wherein the patient is human (page 8, paragraph 3 in particular), and the aliquot of modified mammalian blood is the patient's own blood (page 12, paragraph 4 in particular), of volume from about 0.01-400 ml (pages 8, 13, in particular).

Similarly, US Patent '954 teaches a method of an autoimmune diseases in a mammalian patient, including inflammatory bowel disease and psoriasis, in a mammalian patient comprises administering to the patient stressed mammalian blood cells (see the entire document, column 1, and overlapping columns 7 –8 in particular) . The US Patent '954 teaches that stress blood cells have been extracting from the patient an aliquot of blood of volume, contacting the aliquot of blood, extracorporeally subject to at both oxidative conditions, ultraviolet radiation and heat stress simultaneously. (see column 6, in particular). The US Patent '954 teaches that oxidative environment, such as a mixture of ozone, wherein an ozone content from about 0.5 to about 100 μg/ml and oxygen bubbled through the blood aliquot, from about 0.5 to 60 min (see overlapping columns 7-8 and Claim 5 in particular). The US Patent '954 teaches that the flow rate of the gas is applied at about 0.01-2 liters/min. (see column 8 in particular). The US Patent '954 teaches that the temperature stressor is in a range from about 0^0 to about 55° C (see column 7 and claim 4 in particular). The US Patent '954 teaches that UV stessor is UV-c radiation (see column 8 in particular). Wherein the patient is human, and the aliquot of modified mammalian blood is the patient's own blood of volume from about 0.01-400 ml (column 9 and claim 2 in particular).

As evidence by the disclosure of the Specification on page 1, line 5-20, it was well known in the art at the time the invention was made that deficiency of IL-10 results in the development of autoimmune diseases such as psoriasis. Thus, it is apparent that a method of treating autoimmune diseases in a mammalian patient, taught by WO'703 and US Patent '954 is a method for treatment of an IL-10 deficiency-mediated disease.

Claims 36-38 are included because the claimed functional limitation would be inherent properties of the claimed method for treating inflammatory disease, taught by WO ' 703, WO' '703, US Patent '954. The prior art method and the instant claims administering the same treatment, i.e. stressed blood cells to the same mammalian patient thus it would inherently results in the increasing of IL-10 levels in the blood or tissue of a mammalian patient. Mere recognition of latent properties in the prior art does not render known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent

function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. If the prior art structure is capable of performing the intended use, then it meets the claim. When a claim recites using an old composition or structure (e.g. stressed mammalian blood cells) and the use is directed to a result or property of that composition or structure (treatment of an inflammatory disease) then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

The references teaching anticipates the claimed invention.

12. Claims 1-25, 36-38 and 47-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/07463 , U.S. Patent No. 5,980,954 or WO00/06703 as is evidenced by the known fact disclosed in the Specification on page 1, lines 5-20.

The teachings of WO 98/07463 , U.S. Patent No. 5,980,954 and WO00/06703 and the known fact have been discussed, supra.

WO 98/07463 , U.S. Patent No. 5,980,954 or WO00/06703 do not explicitly teach a method for treatment of an IL-10 deficiency-mediated disease wherein: (i) the gaseous mixture has an ozone content about 300 μg/ml, as claimed in claim 4; (ii) the temperature stressor is in the range from about –5°C to about 55° C, or from about 37°C to about 44° C or from about 0° to about 36.5° C or from about 10°C to about 30° C or from about 37° to about 55° C as claimed in claims 11-15 accordingly

The claimed temperature ranges overlaps the references ranges taught by WO 98/07463 , U.S. Patent No. 5,980,954 or WO00/06703 . Therefore, the claimed invention is an obvious variation of the reference teachings, absent a showing of unobvious differences. Moreover, it would be conventional and within the skill of the art to determine the optimal ozone content in the gas mixture. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/07463 or U.S. Patent No. 5,980,954 or WO00/06703 as is evidenced by the known fact disclosed in the Specification on page 1, lines 5-20 as applied to claims 1-25, 36-38 and 47-49 above, and further each in view of Toto P., et al (J of Immunology, 2000, v.164, pages 522-529).

The teachings of WO 98/07463 , U.S. Patent No. 5,980,954 and WO00/06703 have been discussed, supra.

WO 98/07463 , U.S. Patent No. 5,980,954 or WO00/06703 and the known fact do not explicitly teach treating pemphigus by administering to the patient stressed mammalian blood cells.

Toto P., et al., teaches that pemphigus is an inflammatory autoimmune disease that can be mediated by deficiency in IL-10 (see enire document, Abstract in particular). Toto P., et al., teaches that administration of IL-10 can be used to treat pemphigus in human (see page 527 in particular).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching Toto P., et al., to those of WO 98/07463 or U.S. Patent 5,980,954 or WO00/06703 to obtain a claimed method for treating pemphigus by administering to the patient stressed mammalian blood cells .

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because pemphigus is one species of inflammatory autoimmune disease that is mediated by deficiency in IL-10 as taught by Toto P., et al. Said disease can substitute another species of inflammatory and autoimmune disease that is mediated by IL-10 deficiency, for example psoriasis that can be treated by the method taught by WO 98/07463 , U.S. Patent No. 5,980,954 or WO00/06703 each comprising administering an aliquot of blood which has been treated *ex-vivo* with a stressor. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected

beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-26, 36-38 and 47-49 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of copending Application No. 10/002,634 in view of Immune Support (2004, 1-7) and Toto P., et al.

Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 1-10 of copending Application No. 10/002,634 recites a method for treatment or prophylaxis of chronic fatigue syndrome in a patient comprising administering an aliquot of blood which has been treated *ex-vivo* with a stressor, wherein a stressor is oxidative condition heat stress and ultraviolet radiation, wherein : (i) oxidative conditions comprise bubbling ozone from about 0.5 to about 60 min, as climed in claim 6; (ii) ozone content in the mixture from about 0.1 to 100 μg/ml ,as claimed in claim 7; (iii) the temperature stressor is in the range from about 40° C to about 55°C, as claimed in claim 9; and the volume of whole blood from about 0.1 to about 400mls, as claimed in claim 10.

Claims 1-10 of copending Application No. 10/002,634 do not explicitly recites the process of treating an IL-10 deficiency-mediated disease wherein: (i) said disease is pemphigus, comprising administering to said patients an effective amount of stressed mammalian blood, claimed in claim 26 or (ii) the gaseous mixture has an ozone content about 300 μg/ml, as claimed in claim 4; (iii) the temperature stressor is in the range from about –5°C to about 55° C, or from about 37°C to about 44° C or from about 0° to about 36.5° C or from about 10°C to about 30° C or from about 37° to about 55° C as claimed in claims 11-15 accordingly.

Immune Support teaches that chronic fatigue syndrome is an inflammatory disease that is characterized by low levels of IL-10.

Toto P., et al., teaches that pemphigus is an inflammatory autoimmune disease that can be mediated by deficiency in IL-10 (see enire document, Abstract in particular).

Thus it would have been obvious to a person of ordinary skill in the art at the time the invention was made that method of treating chronic fatigue syndrome , comprising administering to said patients an effective amount of mammalian blood which has been treated *ex-vivo* with a stressor, taught by Copending Application No. 10/002,634 can be used to treat pemphigus because both diseases are inflammatory disorders associated with IL-10 deficiency as taught by Immune Support al and Toto et al.

The claimed temperature ranges overlaps the references ranges of copending Application 10/002,634 . Therefore, the claimed invention is an obvious variation of the reference teachings, absent a showing of unobvious differences. Moreover, it would be conventional and within the skill of the art to determine the optimal ozone content in the gas mixture. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. No claim is allowed.

17. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michail Belyavskyi, Ph.D.
Patent Examiner
Technology Center 1600
January 17, 2005

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600